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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 31

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/977,787	Applicant(s) MIZZEN ET AL.	
	Examiner Mary K Zeman	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,57-59 and 61-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54,57,59,61-65 and 68-87* is/are rejected.

7)☐ Claim(s) *58,66 and 67* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

The supplemental after-final amendment, filed 8/7/01, has been entered and considered. Claims 55, 56 and 60 have been canceled. Claims 54, 57-59 and 61-67 have been amended, and claims 68-87 have been added.

The declaration filed under 1.131 filed with the response is effective to overcome rejections made over Suzue et al..

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 54, 57, 59, 61-65 and 68-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young (WO 94/29459, PTO-1449 AL2) in view of Smith et al.(US 5,858,368)

The above-rejected claims are drawn to fusion proteins comprising a heat shock protein in fusion with an antigen of the influenza virus, wherein the fusion protein elicits a cell-mediated immune response.

Young (WO 94/29459, PTO-1449 AL2) discloses fusion proteins of bacterial stress proteins with antigens, proteins or peptides. The heat shock proteins can be bacterial, specifically from mycobacteria. Specific antigens disclosed by Young include hsp60, hsp65, hsp70, etc. Young notes that heat shock proteins are known in the art to induce T-cell mediated

immune responses when administered to a subject. At pages 21-22, Young specifies that the heat shock protein can be produced recombinantly, and specifically that it can be produced recombinantly in fusion with an antigen. The antigens, proteins and/or peptides can be selected from viruses, pathogens, neoplasias "any substance against which an immune response is desired." Young exemplifies a fusion protein between hsp70 and HIV p24 antigen. This fusion protein (in combination with an acceptable diluent or buffer) was shown to induce a humoral response to the viral antigen that was more than 2 fold greater than compared to the viral antigen alone, and clearly induced a T cell response to the viral antigen. Young does not specifically disclose influenza antigens.

Smith et al. (US 5,858,368) discloses recombinant fusion proteins wherein influenza hemagglutinin antigens are produced in fusion with heterologous sequences (columns 8-10). The preferred heterologous signals are baculovirus signal sequences, which are used to replace the natural HA hydrophobic signal sequence. Smith et al. disclose that the influenza HA fusion proteins are useful for induction of an immune response to the HA antigen. Further, the fusion proteins are easier to produce in large quantities in comparison to purification from traditional influenza culturing methods which required adapted virus, and chicken eggs. These recombinant fusion proteins (in pharmaceutical compositions) are highly immunogenic, and provoke a potent, protective humoral immune system response (neutralizing antibodies).

It would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza HA antigen of Smith et al. One of skill in the art would have been motivated to make such a change in order to provoke a response from both the humoral immune system, and the cellular immune system. The most effective vaccines activate both parts of the immune system. Young discloses that the heat shock protein induces a clear T cell response to the antigen that is in fusion, and Smith et al. disclose that influenza HA antigen, made recombinantly and in fusion, can provoke a strong, protective humoral immune system response. One of skill in the art would have had a reasonable expectation of success in making the fusion construct between hsp70 and the influenza HA, as only routine cloning skill are required. Young provides the necessary hsp sequences and vectors, and Smith et al. provide the influenza HA sequences. Therefore, the invention as a whole is

prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 75-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young (WO 94/29459, PTO-1449 AL2) in view of Lathe et al.(US 6,007,806)

The above-rejected claims are drawn to fusion proteins comprising a heat shock protein in fusion with an antigen of the HPV virus, wherein the fusion protein elicits a cell-mediated immune response.

Young (WO 94/29459, PTO-1449 AL2) discloses fusion proteins of bacterial stress proteins with antigens, proteins or peptides. The heat shock proteins can be bacterial, specifically from mycobacteria. Specific antigens disclosed by Young include hsp60, hsp65, hsp70, etc. Young notes that heat shock proteins are known in the art to induce T-cell mediated immune responses when administered to a subject. At pages 21-22, Young specifies that the heat shock protein can be produced recombinantly, and specifically that it can be produced recombinantly in fusion with an antigen. The antigens, proteins and/or peptides can be selected from viruses, pathogens, neoplasias, or "any substance against which an immune response is desired." Young exemplifies a fusion protein between hsp70 and HIV p24 antigen. This fusion protein (in combination with an acceptable diluent or buffer) was shown to induce a humoral response to the viral antigen that was more than 2 fold greater than compared to the viral antigen alone, and clearly induced a T cell response to the viral antigen. Young does not specifically disclose HPV antigens.

Lathe et al. (US 5,858,368) discloses recombinant fusion proteins wherein HPV antigens are recombinantly produced for use in a vaccine against HPV-induced tumors. The preferred HPV antigens include E6 and E7 (columns 16-18). Lathe et al. disclose that the HPV E6 and E7 proteins are useful for induction of an immune response to the HPV antigen. Further, the recombinant proteins are easier to produce in large quantities in comparison to purification from viral culture. These proteins (in pharmaceutical compositions) are immunogenic, and used by Lathe to treat and/or prevent tumors of HPV origin. This regression and/or prevention of HPV tumors shows that the E6 and the E7 are each able to activate immune effector cells necessary for the elimination and/or prevention of the tumor cells.

It would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the HPV E6 or E7 antigen of Lathe et al. One of skill in the art would have been motivated to make such a change in order to provoke a response from both the humoral immune system, and the cellular immune system. The most effective vaccines activate both parts of the immune system. Young discloses that the heat shock protein induces a clear T cell response, and a strong humoral response to the antigen that is in fusion, and Lathe et al. disclose that HPV E6 and E7 antigen, made recombinantly, can provoke a strong, immune system response. One of skill in the art would have had a reasonable expectation of success in making the fusion construct between hsp70 and the HPV E6 or E7, as only routine cloning skill are required. Young provides the necessary hsp sequences and vectors, and Lathe et al. provide the HPV E6 and E7 sequences. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Claims 58, 66 and 67 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can generally be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028.

The official fax number for this Art Unit is (703) 308-4242. An unofficial fax number, direct to the Examiner is 703 746 5279. Please call prior to use of this number.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose telephone number is (703) 305-3524.

mkz
8/20/01

MARY K. ZEMAN
PATENT EXAMINER
AU 1631